Symptoms in Pediatric Asthmatics and Air Pollution: Differences in Effects by Symptom Severity, Anti-inflammatory Medication Use and Particulate Averaging Time

Ralph J. Delfino,[1] Robert S. Zeiger,[2,3] James M. Seltzer,[2,4] and Donald H. Street[5]

[1]Epidemiology Division, Department of Medicine, University of California, Irvine, CA 92697 USA; [2]Department of Pediatrics, University of California, San Diego School of Medicine, San Diego, CA 92103 USA; [3]Department of Allergy, Southern California Permanente Medical Group, San Diego, CA 92111 USA; [4]Health Advance Institute, San Diego, CA 92123 USA; [5]Bayer Corporation, Allergy Products, Independence, OR 97351 USA

Experimental research in humans and animals points to the importance of adverse respiratory effects from short-term particle exposures and to the importance of proinflammatory effects of air pollutants, particularly O_3. However, particle averaging time has not been subjected to direct scientific evaluation, and there is a lack of epidemiological research examining both this issue and whether modification of air pollutant effects occurs with differences in asthma severity and anti-inflammatory medication use. The present study examined the relationship of adverse asthma symptoms (bothersome or interfered with daily activities or sleep) to O_3 and particles <10 µm (PM_{10}) in a Southern California community in the air inversion zone (1200–2100 ft) with high O_3 and low PM (R = 0.3). A panel of 25 asthmatics 9–17 years of age were followed daily, August through October 1995 (n = 1,759 person-days excluding one subject without symptoms). Exposures included stationary outdoor hourly PM_{10} (highest 24-hr mean, 54 µg/m^3, versus median of 1-hr maximums, 56 µg/m^3) and O_3 (mean of 1-hr maximums, 90 ppb, 5 days >120 ppb). Longitudinal regression analyses utilized the generalized estimating equations (GEE) model controlling for autocorrelation, day of week, outdoor fungi, and weather. Asthma symptoms were significantly associated with both outdoor O_3 and PM_{10} in single pollutant- and co-regressions, with 1-hr and 8-hr maximum PM_{10} having larger effects than the 24-hr mean. Subgroup analyses showed effects of current day PM_{10} maximums were strongest in 10 more frequently symptomatic (MS) children: the odds ratios (ORs) for adverse symptoms from 90th percentile increases were 2.24 [95% confidence interval (CI), 1.46–3.46] for 1-hr PM_{10} (47 µg/m^3); 1.82 (CI, 1.18–2.81) for 8-hr PM_{10} (36 µg/m^3); and 1.50 (CI, 0.80–2.80) for 24-hr PM_{10} (25 µg/m^3). Subgroup analyses also showed the effect of current day O_3 was strongest in 14 less frequently symptomatic (LS) children: the ORs were 2.15 (CI, 1.04–4.44) for 1-hr O_3 (58 ppb) and 1.92 (CI, 0.97–3.80) for 8-hr O_3 (46 ppb). Effects of 24-hr PM_{10} were seen in both groups, particularly with 5-day moving averages (ORs were 1.95 for MS and 4.03 for LS; p<0.05). The largest effects were in 7 LS children not on anti-inflammatory medications [5-day, 8-hr PM_{10}, 9.66 (CI, 2.80–33.21); current day, 1-hr O_3, 4.14 (CI, 1.71–11.85)]. Results suggest that examination of short-term particle excursions, medication use, and symptom severity in longitudinal studies of asthma yields sensitive measures of adverse respiratory effects of air pollution. *Key words*: asthma, epidemiology, longitudinal data analysis, ozone, panel study, particulate air pollution. *Environ Health Perspect* 106:751–761 (1998). [Online 22 October 1998]
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Recent experimental findings in humans indicate adverse respiratory effects from short-term exposures to particulate air pollutants delivered over 1 to several hours (*1*). Therefore, it is biologically plausible that short-term excursions of particulate air pollution in communities could have adverse impacts on the respiratory health of susceptible individuals. However, in the experimental work to date, averaging time has not been subjected to direct scientific evaluation. For example, it is not known whether, for any given particle type, a greater or lesser effect on respiratory outcomes would occur for equivalent delivered doses given over shorter times (1 to several hours) as compared with longer times such as 24 hr (current EPA averaging time for regulatory monitoring). Also, there is a lack of epidemiological research examining respiratory effects from peak particle exposures since most have relied on daylong averaging times, namely 24-hr means or occasionally 12-hr diurnal means. It has been suggested that the epidemiologic findings showing adverse effects of particulate matter <10 µm (PM_{10}) levels below the current U.S. National Ambient Air Quality Standards (NAAQS) could be partly explained by unmeasured short-term particle excursions that are captured somewhat by 24-hr averages (*2*). In fact, prior to recent EPA regulatory proposals for tightening the NAAQS for PM and O_3, the EPA's Clean Air Science Advisory Committee advised the EPA to give a scientific rationale for the 24-hr PM_{10} averaging time in the NAAQS (*3*). To our knowledge, there are no epidemiologic studies reported in the peer-reviewed literature that have analyzed respiratory effects of peak particle concentrations.

The current controversy over the EPA's regulatory changes center on the argument that improved standards are needed to protect the most susceptible subgroups in the U.S. population such as asthmatics. A recent review of the epidemiologic literature on PM and asthma suggests that mean levels of PM in North America and Europe, often within the previous NAAQS, may be responsible for increases of 2–5% in asthma hospital admissions and 5–10% in asthma emergency room (ER) visits (*4*). Supporting experimental data for asthma exacerbations from PM are largely indirect, but suggest that particle deposition in the lower respiratory tract can cause inflammation, diminished mucociliary clearance and macrophage function, and adverse changes in lung function (*5*). The role of O_3 in airway inflammation is more clearly supported by experimental evidence showing greater increases in O_3-induced inflammatory markers in bronchoalveolar lavage (BAL) fluid in asthmatics than in normal subjects (*6*). Such an effect has been hypothesized to enhance allergen-induced bronchoconstriction in asthmatics (*7*). Clearly, there is a scientific need for explanations of epidemiologic findings of adverse effects on asthmatics by both PM and O_3 at low ambient concentrations.

Address correspondence to R.J. Delfino, Epidemiology Division, Department of Medicine, 224 Irvine Hall, University of California, Irvine, CA 92697-7550 USA.

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Because asthmatics differ greatly with respect to disease severity, which is to a large extent dependent on the magnitude of underlying pulmonary inflammation, the proinflammatory effects of air pollutants will likely vary in more versus less severe asthmatics. Air pollutant effects may also differ depending on whether an asthmatic is taking anti-inflammatory medications, including inhaled corticosteroids, which are now considered to be the most effective front-line therapy for recurrent chronic asthma (*8*). Therefore, reported effects of pollutants on asthmatic populations in epidemiologic studies may underestimate effect magnitudes in particularly susceptible subgroups.

The objective of this study is to examine the relationships of daily asthma severity to 1-hr maximum and 8-hr maximum PM_{10} and O_3, and 24-hr mean PM_{10} among 24 nonsmoking pediatric asthmatics living in nonsmoking households. Outdoor concentrations of PM_{10} were measured with a tapered-element oscillating microbalance (TEOM; Rupprecht and Patashnick, Inc., Albany, NY), an inertial instrument that measures particle mass in real time (*9*). The strength of association will be compared between 1) the different averaging times; 2) subjects having varying magnitudes of asthma symptom severity during follow-up; and 3) asthmatics taking and not taking anti-inflammatory medications. Comparisons 2 and 3 aim to identify potentially susceptible subgroups of asthmatics.

Materials and Methods

Research design. The present investigation is a panel study, a longitudinal study characterized by repeated measurements of health outcomes and exposures in individuals. Whittemore and Korn (*10*) originally adapted the panel study for a study that showed acute adverse associations of O_3 and particulate air pollution with asthma attacks in a Los Angeles, California, cohort followed in the 1970s. The present study examines the relationship of daily diary reports of asthma symptom severity to airborne environmental risk factors measured at a central outdoor site in Alpine, California, from 1 August to 30 October 1995.

The panel design makes it possible to determine the temporality of associations (i.e., the putative cause precedes the outcome) and to observe individual patterns of change in exposure and response (*11*). These advantages are particularly well suited to the study of illnesses such as asthma with acute-on-chronic patterns of change. Other major advantages of the panel design are that the use of daily diaries reduces the likelihood of recall bias, given the proximity of events, and that health effects can be modeled with each subject serving as his or her own control over time. The last advantage in design shares similar features to the crossover clinical trial in that both study designs are statistically efficient (enhanced signal-to-noise ratio) because multiple treatment or exposure conditions are studied in each subject and variability in exposure–response relationships due to between-subject characteristics is controlled for by design (*12*). The last advantage is due to a reduction in the variability of the response variable without reductions in the magnitude of the exposure–response relationship, thereby enhancing power and precision (*11*). These advantages are largely lost when individual responses on each day of observation are aggregated into time series with variable numbers of participants from day to day.

Study population. The region studied is a semirural area of Southern California around the small town of Alpine, an inland community of approximately 12,000 people living within the air inversion mixing zone (town at elevation of 1800 ft, range 1200–2100 ft). This zone typically has high O_3 concentrations due to transport of urban air masses from San Diego and Los Angeles, with photochemical oxidation of nitrogen oxides and hydrocarbons. The community was originally targeted for research to maximize the ability to isolate the independent effect of O_3 from that of particulate air pollutants. In other air pollution studies of urban areas, this task has been difficult due to high pollutant covariation. This separation was possible with Alpine data because of high O_3 and low PM_{10} concentrations, as well as weak correlations between the two pollutants (between-pollutant $R \leq 0.32$ for various averaging times).

The institutional review board of San Diego State University approved the study protocols. Informed written consent was obtained from all children and adolescents and one of their legal guardians. Recruitment of subjects was done with newspaper advertisements, with the assistance of the Alpine School District nurse covering all four grade schools and with referrals from the Kaiser Permanente Health Plan, Inc., San Diego Area, Department of Allergy. Monetary incentives were an essential component of both recruitment and maintenance of compliance during follow-up. Subjects were not told what specific exposures were being monitored, but were simply told that the study involved the examination of environmental agents including outdoor allergens.

Eligibility criteria included 1) physician-diagnosed asthma with a minimum history of 1 year; 2) asthma exacerbations during several weeks of the warm seasons (March through October) requiring the use of prescribed asthma medications; 3) ages between 9 and 18 years; and 4) a home and school address in Alpine or adjacent areas. Also, smokers and subjects exposed to environmental tobacco smoke at home were excluded to reduce the influence of this risk factor. Eligibility criterion number 2 was intended to target subjects having frequent episodes of asthma symptoms requiring medication and adversely impacting the subject's daily life. This enhances the representation of asthma populations with a more frequent incidence of clinically severe outcomes that have been associated with air pollution elevations (e.g., asthma hospital admissions). Asthma mortality also occurs predominantly among this group (*8*). Very mild asthmatics with infrequent exacerbations, particularly young children, are more likely to have their asthma exacerbations with respiratory infections (*13*). Therefore, the targeted population has particular relevance to the public health impact of air pollutants.

Twenty-five asthmatics 9–17 years of age agreed to participate and were interviewed and trained. One 14-year-old girl dropped out at 69 out of 91 days, but her data were retained for analysis. Since subjects were recruited into the third week of September, the minimum to maximum potential person-days of observation was 42–91.

Asthma symptom score. In the evening, subjects recorded the level of asthma symptom severity for the previous 24 hr. Subjects were followed-up weekly during the first 2–3 weeks, then biweekly at their home for validity checks to insure the accuracy of diaries and compliance with the study protocol. Also, questions by participants were regularly answered face to face.

Daily diary questions concerning asthma symptoms emphasize the impact of the clinical severity of asthma on the normal daily activities that are typical for each individual. Subjects received training in interpreting the scoring system in this manner. Because the complex of symptoms recognized or experienced by asthmatics differs from one person to another, the approach used combines the rating of various symptoms into one score that relates, in part, to the impact of asthma on a subject's daily well-being. Asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness) were rated by the subjects in terms of their combined severity on a scale from 0 to 5. This classification contrasts a commonly used approach of dichotomizing each individual symptom into present or absent. The clinical severity of asthma in many asthmatics could be obscured by a symptom-specific approach.

Subjects classified the six levels of asthma severity as 0, no asthma symptoms present; 1, asthma symptoms present but caused no discomfort; 2, asthma symptoms caused discomfort but did not interfere with daily activities or sleep; 3, asthma symptoms interfered somewhat with daily activities or sleep; 4, asthma symptoms interfered with most activities and may have required that the participants stay home in bed, return home early from school, or call a doctor or nurse for advice; 5, asthma symptoms required going to a hospital, ER, or outpatient clinic.

The asthma symptom score was used to create the response variable representing the occurrence of asthma symptoms that have an adverse impact on the subject's well-being. This is a dichotomous variable derived as follows: no asthma symptoms or symptoms not bothersome (score 0 or 1) versus symptoms that are bothersome or interfere with daily activities (score >1). This cut point was chosen for the following reasons. First, a cut point between 0 and 1 was not used because symptoms not considered by the subject to be bothersome have a good chance of not being clinically meaningful in the absence of contemporaneous lung function measurements indicating an acute deficit. Second, only 10% of the symptom observations were >2; of these observations, only 17 person-days had a score of 4, and only 3 person-days had a score of 5. Separate analysis of these more clinically severe outcomes was not informative, possibly due to limited statistical power. In one mildly symptomatic subject, all binary values were 0. Consequently, the data analysis excludes this subject. The remaining 24 participants contributed 1,759 person-days of symptom observations for the analysis out of a potential of 1,895 person-days.

Environmental variables. Continuous monitoring of outdoor O_3 was conducted using UV photometry at a stationary outdoor monitoring station located centrally in Alpine and operated by the San Diego Air Pollution Control District. The PM_{10} concentrations were recorded with a TEOM in real-time (*9*) located at the same site. The PM_{10} data were used as 1-hr averaged data, similar to standard O_3 monitoring, but in contrast to the standard 24-hr filter-pack PM_{10}. The TEOM is certified by the EPA for measuring PM_{10} concentration. It incorporates an inertial balance that measures the mass on an exchangeable filter cartridge by monitoring frequency changes of a tapered element. The TEOM sampler inlet was operated at 16.7 l/min and the inlet air stream was heated to a constant 50°C to keep water in the vapor phase. We did not collect samples for daily particle composition or size fractions. Sampling, analysis, and data processing protocols for PM_{10} were carried out as part of another ongoing project at the University of Southern California (*14*). Twenty contiguous days from 10–29 August were missing because of TEOM equipment malfunction. Hourly temperature, relative humidity, and wind speed were also measured at the stationary outdoor site.

There were low concentrations of outdoor pollen during the dry part of the year (August–October) in this semiarid desert region (mean, 55 pollen grains/m^3). Therefore, bioaerosol analyses focus on fungi, many of which thrive on the decaying biomass of the region's chaparral. Measurements of fungal spores were made at the stationary outdoor site using the Burkard 7-day recording volumetric spore collector with a sample flow rate of 10 l/min (Burkard Manufacturing Co. Ltd., Rickmansworth, Hertfordshire, England). The methods of sample collection and quantification have been previously described (*15*). Fungal spores and hyphal fragments were microscopically counted and identified by 12-hr segments from 900 to 2100 hr and from 2100 to 900 hr. The fungal counts were then converted into particles per cubic meter of air for each 12-hr and 24-hr (2100–2100 hr) time period (approximate diary reporting period).

Statistical analysis The analysis began with descriptive statistics, which included time plots for the examination of possible trends in the data. Exposure correlation matrices were constructed to assess the amount of intercorrelation, which could predict potential confounding or collinearity effects in the regression analyses. The regression analysis of pollutant effects on the binary symptom score utilized generalized estimating equations (GEE). The GEE approach was developed by Liang and Zeger (*16*) for nonnormal response data that are discrete and correlated (within-individual clusters). Repeated daily measurements over time in individuals constitute a cluster of observations. The model is conceptually a set of separate regression models on repeated measurements in each individual. Therefore, every subject can act as his or her own control. The GEE models were tested using the logit link in the SAS generalized linear model procedure GENMOD (SAS Institute, Cary, NC). The GENMOD procedure uses a ridge-stabilized Newton-Raphson algorithm to maximize the log likelihood function for the regression parameters.

The GEE approach used is well-suited to panel data because it can be applied to repeated measures that are unbalanced, have unequal numbers of observations in different individuals, or have missing observations; and it accounts for temporally correlated responses and the dependence of repeated observations in single individuals. Serial correlation was accounted for with AR1 parameters to control autocorrelation of residual errors, a potential source of bias.

Analyses were also performed on various subgroups as an approach to identifying potentially susceptible populations of asthmatics. These groups were 1) less versus more frequently symptomatic asthmatics and 2) asthmatics taking versus not taking regularly scheduled anti-inflammatory medications. For the first case, the panel was split into two groups: one with less frequent symptoms (LS), defined as <20% of days with asthma symptoms that were bothersome or interfered with daily activities, and another with more frequent symptoms (MS), defined as ≥20% of days with such symptoms. These two groups were defined as such because the subjects fell into two relatively distinct groups from examination of frequency distributions of the ordinal symptom scores in each subject. When the average symptom scores for each day of study were compared between the two groups, two minimally overlapping normal distributions were observed. Also, using 0/1 as a cut point on the ordinal symptom scale, the LS group is close to the National Heart Lung and Blood Institute (NHLBI) criteria for defining asthma severity as mild intermittent (symptoms ≤2 times/week), and the MS group is close to the NHLBI criteria for mild persistent or worse severity (symptoms >2 times/week) (*8*). There were no severely asthmatic subjects with constant symptoms, such as those requiring long-term oral steroids.

Delayed air pollutant effects were examined by regressing symptoms on pollution levels measured on up to 6 days before the day of symptom reporting. Moving averages combining air pollution levels on current and lag days were also tested after examining the distribution of individual day lag effects (*17*). Because pollutants were measured on 6 days before the start of the study, it was possible to test lag effects from the first day of follow-up. However, lags and moving averages for PM_{10} were missing for up to 5 days following the time the TEOM was malfunctioning. Several lag days for PM_{10} were significant in the regression models, including 1 and 4 days before the day of symptom reports. The largest and most robust effects were found for 5-day moving averages of 1-hr, 8-hr, and 24-hr PM_{10}. Therefore, results focus on effects of current day and 5-day moving averages of PM_{10}.

We previously showed that outdoor fungal aerosols have adverse effects on asthma

Table 1. Descriptive statistics for asthmatic subjects, August–October 1995 in Alpine, California

Group	Mean age (range)	No. males/ females	Mean daily symptom score ± SD	No. subjects on anti-inflammatory medications (%)	Mean daily as-needed β-agonist inhaler puffs ± SD
MS[a]	13.1 (9–16)	7/3	1.40 ± 1.18	1	1.21 ± 1.58
LS[b]	12.7 (10–17)	8/6	0.40 ± 0.75	7	1.03 ± 3.33
LS asthmatics on anti-inflammatory medications	11.4 (10–16)	5/2	0.47 ± 0.81	7	2.36 ± 4.91
LS asthmatics not on anti-inflammatory medications	14.0 (11–17)	3/4	0.33 ± 0.68	0	0.14 ± 0.53
Overall (n = 24)	12.9 (9–17)	15/9	0.80 ± 1.07	8 (33)	1.11 ± 2.72

Abbreviations: MS, more symptomatic; LS, less symptomatic; SD, standard deviation.
[a]MS asthmatics were defined as having ≥20% of days with asthma symptoms that were bothersome or interfered with daily activities (10 asthmatics).
[b]LS asthmatics were defined as having <20% of days with asthma symptoms that were bothersome or interfered with daily activities during follow-up (14 asthmatics).

Table 2. Descriptive statistics for daily air pollution and weather measurements, 1 August–30 October 1995 in Alpine, California

Exposure and averaging time	No. obs	Mean ± SD	Min/max	90th Percentile
O_3 outdoor 1-hr max (ppb)[a]	91	90 ± 18	52/135	110
O_3 outdoor 8-hr max (ppb)	91	73 ± 15	44/110	90
PM_{10} 1-hr max (μg/m^3)[b]	71	57 ± 16	30/108	77
PM_{10} 8-hr max (μg/m^3)	71	43 ± 12	23/73	59
PM_{10} 24-hr mean (μg/m^3)	71	31 ± 8	16/54	42
Fungi 12-hr daytime mean (particles/m^3)	91	3,043 ± 1,818	844/15,594	4,510
Fungi 24-hr mean (particles/m^3)	91	2,676 ± 1,263	1,191/9,094	3,812
Temperature 1-hr max (°F)	91	88 ± 8	72/103	98
Relative humidity 24-hour mean (%)	91	48 ± 19	16/89	82
Wind speed 12-hr mean (mph)[c]	91	4.1 ± 0.6	2.7/5.3	4.8

Abbreviations: obs, observations; SD, standard deviation; min, minimum; max, maximum; mph, miles per hour.
[a]The stationary site outdoor monitor was the Alpine site operated by the San Diego Air Pollution Control District.
[b]Twenty days are missing because of tapered-element oscillating microbalance equipment malfunction.
[c]Levels for the 12-hr sampling period were averaged from 800 to 2000 hr.

symptoms in previous panel studies in San Diego and Alpine (*15,18,19*). However, the present analysis focuses on air pollutants, and total fungal particles will be used as a control variable for air pollutant effects following an examination of fungi–pollutant interactions. Our previous analyses of asthma and outdoor fungi have been extensive, involving numerous fungal types, and stratified by the allergic sensitization of subjects (*15*). Therefore, we will present such detailed analyses on this cohort in a later report.

A local brush fire occurred during the last 3 days when the TEOM sampler was malfunctioning (27–29 August). Regression analysis including an indicator variable for this event showed no association with asthma symptoms and no confounding of O_3 models. Possible reasons for no associations include the limited statistical power of modeling this relatively brief event and reports from subjects and their parents that outdoor activity was restricted by choice, which may have diminished smoke exposure. Models were also tested for confounding by day of week trends, temperature, relative humidity, and wind speed. Confounding was indicated by at least a 15% change in the parameter estimate for the pollutant. The analysis of wind speed was intended to examine the possible importance of wind-blown dust to particle effects. Deviance statistics for GEE models were used to assess the fit of various models. Comparisons of the fit of single versus co-pollutant models for O_3 were initially restricted to days with nonmissing PM_{10}.

Results

Subject characteristics. Most subjects were white, non-Hispanic except for four Hispanics, one African American, and one Asian. This distribution reflects the racial/ethnic make-up of the Alpine community. Table 1 shows the characteristics of the asthmatic subjects by the groups analyzed. Eight subjects were using daily inhaled anti-inflammatory medications (six subjects were on corticosteroids, one on cromolyn and one on nedocromil). Only one pediatric MS asthmatic was on an anti-inflammatory medication (nedocromil), leaving insufficient power to make a comparison of anti-inflammatory users versus nonusers. Seven asthmatics on anti-inflammatory medications were LS asthmatics, suggesting that some of the LS asthmatics had less frequent symptoms because of their treatment regimen. The medicated LS subjects had a similar average symptom score but used more as-needed β-agonists and were younger. The one LS subject with all binary symptom values = 0 was a 14-year-old white male taking virtually no medication during the study (not shown in Table 1). Other characteristics include a 2:1 ratio of males to females, which reflects the typical pediatric asthma distribution. The ratio was higher in MS asthmatics and in LS asthmatics on anti-inflammatory medications.

Exposures. Exposures are described in Table 2. These concentrations of O_3, PM_{10}, and fungi are typical for the warm seasons in Alpine and are similar to our previous Alpine panel studies (*15,19*). During this warm and dry period, only 5 of 91 days had O_3 levels over 120 ppb (previous NAAQS). The hourly PM_{10} data showed very different concentration profiles depending on the averaging time (Table 2). For instance, the highest 24-hr mean PM_{10} measurement was 54 μg/m^3 as compared with the median of 1-hr maximum PM_{10} of 56 μg/m^3. Figure 1 also shows this difference over time. The highest PM_{10} hourly exposures were from 900 to 1900 hr (>68 μg/m^3) with the highest hourly peaks largely occurring between 1300 and 1600 hr (80–108 μg/m^3). A similar distribution for peak hours of O_3 concentrations was found. Outdoor fungal particle concentrations were moderate, with higher levels during the daytime.

Table 3 shows the correlation between the different exposures. The correlation between PM_{10} and O_3 was low (≤0.32 for various averaging times), in contrast to warm periods in most urban areas. This prevented major problems of multicollinearity in linear regression. Another departure from patterns commonly reported for urban aerosols is the lack of correlation of PM_{10} to temperature or relative humidity. As expected for Southern California, O_3 is often higher on hotter and dryer days. Daytime average wind speed was weakly and inversely correlated with PM_{10}, suggesting that wind-blown dust and its associated coarse particle fraction ($PM_{2.5-10}$) was not a major contributor to PM_{10} mass. Maximum hourly wind speed and 24-hr mean wind speed were more weakly, but still inversely, correlated with PM_{10} variables (not shown). It is likely that cool offshore winds from the Pacific Ocean (indicated by wind direction) led to cleaner air masses.

Regression analysis. For the GEE analysis, the magnitude of effect is expressed as the odds of asthma symptoms for a 90th percentile increase in the pollutant from its minimum level. In the analysis of the whole group of 24 subjects, asthma symptoms were significantly associated with both PM_{10} and O_3 (Table 4). The GEE models adjusted for confounding day of

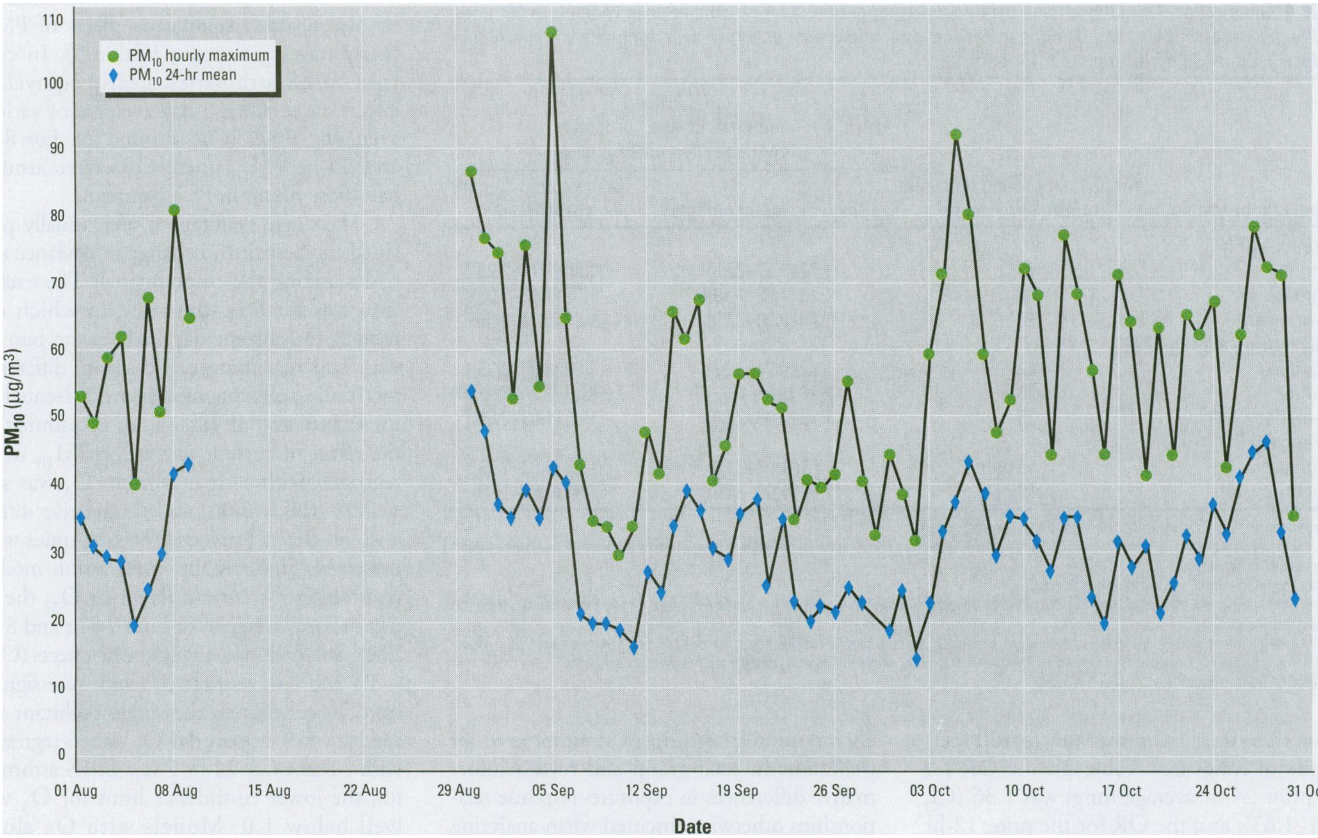

Figure 1. Time plot of daily tapered-element oscillating microbalance (TEOM) PM_{10} in the Alpine Asthma Panel Study, August to October 1995: comparison of maximum hourly with 24-hr average PM_{10}.

Table 3. Air pollution and weather correlation matrix[a] 1 August–30 October 1995 in Alpine, California

	8-hr max O_3	1-hr max PM_{10}	8-hr max PM_{10}	24-hr mean PM_{10}	12-hr daytime fungi	24-hr mean fungi	Maximum temperature	24-hr mean relative humidity	12-hr daytime wind speed
1-hr max O_3	0.90#	0.26*	0.31**	0.31**	0.07	0.16	0.54#	-0.31**	0.07
8-hr max O_3		0.20	0.26*	0.32**	0.07	0.16	0.57#	-0.41#	0.13
1-hr max PM_{10}			0.88#	0.76#	0.24*	0.20	0.10	-0.05	-0.14
8-hr max PM_{10}				0.89#	0.19	0.17	0.07	-0.03	-0.24*
24-hr PM_{10}					0.19	0.22	0.10	0.02	-0.17
12-hr fungi						0.90#	-0.03	0.10	-0.11
24-hr fungi							0.02	0.02	-0.10
Max temperature								-0.70#	0.57#
24-hr relative humidity									-0.42#

Max, maximum.
[a]Pearson correlation coefficients (*p*-value) for 91 ozone observations and 71 PM_{10} observations.
*$p<0.05$; **$p<0.01$; #$p<0.001$.

week trends due to both higher average symptoms and PM_{10} on weekdays than on weekends. Models also adjusted for maximum temperature, which was inversely associated with symptoms [β = -0.021, standard error (SE) = 0.013], consistent with our previous investigation in Alpine (*15*). There was no confounding of PM_{10} or O_3 effects by minimum or average relative humidity, which were not associated with symptoms. Symptoms were not significantly associated with wind speed using any averaging time, and wind did not confound PM_{10} or O_3 effects. Parameter estimates were actually negative for asthma symptoms and wind speed.

Table 4 shows that relative pollutant effect sizes for particles measured on the same day as symptom reports were 1-hr $PM_{10} \cong$ 8-hr PM_{10} >24-hr PM_{10}. The odds ratio (OR) for current day 24-hr PM_{10} was nonsignificant in contrast to highly significant effects for 1-hr and 8-hr PM_{10} averaging times ($p<0.005$). Co-regression of O_3 with PM_{10} did not notably change the effect magnitudes or relative differences in averaging time for PM_{10}. Parameter estimates for 5-day moving averages of 1-hr, 8-hr, and 24-hr PM_{10} were larger than the current day PM_{10} (Table 4). These associations were only significant for 8-hr and 24-hr averaging times. The largest effect was for 5-day 8-hr maximum PM_{10} [OR = 2.25; 95% confidence interval (CI), 1.24–4.07]. These effects were virtually unchanged when co-regressing with O_3.

There were also significant effects of both current day 1-hr and 8-hr O_3, with little difference in the magnitude of risk. Co-regression with current day 1-hr maximum PM_{10} showed similar O_3 effect sizes, but confidence limits were below 1. However, co-pollutant models exclude 20 days with missing PM_{10} and are not strictly comparable to single pollutant O_3 models. The comparison to a model with O_3 alone, restricted to 71 days with nonmissing PM_{10} data, showed that ORs for O_3 were similar to models for all 91 days (OR = 1.57; CI, 1.01–2.44). There was little difference in O_3 concentrations between these 71 days (mean 90, range 52–135 ppb) and the 20 days with missing PM_{10} data (mean 90, range 68–110 ppb). This suggests that effects of O_3 and PM_{10} were largely independent and the increased standard error for the effect of O_3 was due to minor variance inflation by PM_{10}.

The robustness of the above models was retested accounting for fungal particles. For

Table 4. Odds ratios (ORs) for asthma symptoms[a] among 24 pediatric asthmatics in relation to 90th percentile increases in PM_{10} and O_3 concentrations: dependence on pollutant averaging times in the Alpine, California, Panel Study, 1 August–30 October 1995

		ORs (CI) per increase to 90th percentile concentration of PM_{10} or O_3	
Air pollutant variable	Air pollutant range (minimum to 90th percentile)[b]	Single pollutant models[c]	Models adjusting for co-pollutant[d]
Current day PM_{10}			
1-hr max	47	1.72 (1.23–2.39)[#]	1.63 (1.17–2.28)[#]
8-hr max	36	1.73 (1.22–2.46)[#]	1.59 (1.13–2.23)**
24-hr mean	25	1.47 (0.90–2.39)	1.31 (0.84–2.06)
5-Day moving average PM_{10}			
1-hr max	47	1.82 (0.94–3.47)	1.80 (0.96–3.35)
8-hr max	36	2.25 (1.24–4.07)**	2.15 (1.24–3.75)**
24-hr mean PM_{10}	25	1.73 (1.03–2.89)*	1.65 (1.03–2.66)*
Current day O_3			
1-hr max	58 ppb	1.54 (1.02–2.33)*	1.46 (0.93–2.29)
8-hr max	46 ppb	1.42 (1.00–2.00)*	1.31 (0.88–1.96)

Abbreviations: CI, 95% confidence interval; max, maximum.
[a]The asthma symptom severity score was dichotomized to no symptoms or symptoms not bothersome versus symptoms bothersome or interfering with daily activities.
[b]Values shown are μg/m³ except where indicated.
[c]Single pollutant models involve 71 days for PM_{10} and 91 days for O_3 models; models adjust for day-of-week trends and maximum temperature (lag 0 models).
[d]All PM_{10} co-pollutant models adjust for current day 1-hr max O_3; O_3 co-pollutant models adjust for current day 1-hr maximum PM_{10}. All co-pollutant models are for 71 days with nonmissing PM_{10} data; therefore, single pollutant O_3 models are not strictly comparable.
*$p<0.05$; **$p<0.01$; [#]$p<0.001$.

an increase from the minimum to 90th percentile of fungi (see Table 2), the OR for the prior 24-hr average fungi was 1.36 (CI, 1.11–1.67), and the OR for the prior 12-hr daytime fungi was 1.25 (CI, 1.07–1.45), controlling for day-of-week trends. Fungal particles did not confound effects of any of the expressions of either PM_{10} or O_3.

There was a significant linear time trend over the study period of increasing 8-hr maximum PM_{10} and decreasing 1-hr and 8-hr O_3 ($p<0.05$), but not other expressions of PM_{10} ($p<0.4$) or symptoms ($p<0.2$). When an ordinal variable representing day of study was added to the GEE models, there was no confounding of pollutant effects.

Regression diagnostics using deviance residuals did not reveal any particular person-day observations to be overly influential to model parameters. To assess the influence of individual asthmatics on model parameters, each subject was dropped from the analysis and models were rerun with the remaining 23 of 24 subjects. There were some minor decreases in O_3 parameter estimates for 7 subjects, none of whom were taking inhaled corticosteroids. Three were LS asthmatics (one on cromolyn), and 4 were MS asthmatics (one on nedocromil). The 23-subject ORs ranged from 1.44 to 1.48 ($p<0.07$ to $p<0.1$, respectively) as compared with an OR of 1.54 ($p<0.05$) in the model with all 24 subjects. These subgroup effects are further analyzed below.

The effects of pollutants were re-tested after splitting the panel into two groups based on their symptom frequency during follow-up (LS vs. MS). Table 5 shows models for the relationship of symptoms to air pollutants in each group and reveals informative differences in exposure–response relationships otherwise obscured when analyzing the group as a whole. Findings for single pollutant models in Table 5 are as follows. There were no significant effects of current day 1-hr maximum PM_{10} in the LS asthmatics, whereas the 24-hr average PM_{10} was significant and the 8-hr maximum was of borderline significance. Relative effects of various averaging times for current day PM_{10} in LS asthmatics were the inverse of results for the combined cohort: 24-hr PM_{10} >8-hr PM_{10} >1-hr PM_{10}. The analysis of lagged day PM_{10} effects in LS asthmatics revealed significant associations between symptoms and 5-day moving averages of 1-hr, 8-hr, and 24-hr PM_{10}, with ORs higher than those of any single day, including current day PM_{10} (Table 5). These relationships were only significant for 8-hr and 24-hr averaging times, reflecting results for all subjects. Again, the largest OR was for 5-day 8-hr maximum PM_{10} (OR = 4.84; CI, 1.21–13.33), nearly double that of the 5-day 1-hr PM_{10}, but only somewhat higher than the 5-day 24-hr PM_{10}. Significant effects for current day O_3 were found only in LS asthmatics ($p<0.05$). There were no lag day effects of O_3.

In contrast to LS asthmatic children, but reflecting regression results for the combined cohort, significant effects for current day 1-hr maximum PM_{10} were found in MS asthmatic children ($p<0.0002$). Effects of O_3 on this group were small and not significant. Relative particle effect sizes in MS asthmatics were current day 1-hr PM_{10} >8-hr PM_{10} >24-hr PM_{10}. The analysis of MS asthmatics also revealed significant effects of PM_{10} 5-day moving averages (Table 5). In contrast to LS asthmatics, nearly equivalent effects are seen for 5-day averages of various averaging times (ORs around 2). For 8-hr and 24-hr PM_{10}, these ORs were around half those found in LS asthmatics.

The single pollutant models usually provided the best fit (no change in deviance statistics adding the co-pollutant). The exception was for LS asthmatics, in which the models for current day PM_{10} were best fit with 1-hr maximum O_3 (deviance difference >4.0). Co-pollutant models are presented in the last column of Table 5. In LS asthmatics, the effect of current day 24-hr PM_{10} when regressed with 1-hr maximum O_3 was still $p<0.02$ (OR = 2.08) and the relative differences in effects between averaging times were preserved. Similarly, in co-regression models controlling for current day 1-hr O_3, the 5-day moving averages for both 24-hr and 8-hr PM_{10} still had moderately strong effects (ORs = 3.4 and 4.0, respectively) and were significant. In contrast to the single pollutant O_3 model, when current day O_3 was co-regressed with current day 24-hr PM_{10} in LS asthmatics, the lower confidence limit for O_3 was well below 1.0. Models with O_3 alone restricted to 71 days with nonmissing PM showed that ORs were similar to models for all 91 days, but confidence limits were also well below 1.0 ($p<0.15$) as in the co-pollutant model [1-hr O_3 OR = 2.14 (CI, 0.79–5.76); 8-hr O_3 OR = 1.88 (CI, 0.79–4.52)]. Co-regression of current day 24-hr PM_{10} and 1-hr O_3 led to similar reductions in each of their regression parameters (16% for PM_{10} versus 18% for O_3, or 2.47 to 2.08 , versus 2.14 to 1.76, respectively). As in models for the whole group, this suggests that effects of the two pollutants were largely independent, but in this case, the increased standard error for the effect of O_3 was partly due to a loss of 214 person-days of symptom observations in LS asthmatics when co-regressing with PM_{10}.

In contrast, for MS asthmatics there was little to no change in the parameter estimates for current day O_3 or PM_{10} single pollutant versus co-pollutant models, and both 1-hr maximum PM_{10} (OR = 2.18) and 8-hr maximum PM_{10} (OR = 1.74) remained significant ($p<0.0002$ and $p<0.009$, respectively). Co-pollutant models for 5-day moving averages of 1-hr, 8-hr, and 24-hr PM_{10} (controlling for current day 1-hr O_3) were virtually unchanged from models with PM_{10} alone. Odds ratios for O_3 in MS asthmatics were still small and nonsignificant in co-pollutant models controlling for current day 24-hr PM_{10}.

The models for MS asthmatics adjusted for confounding day of week trends due to higher symptoms and PM_{10} on weekdays than on weekends. There was no such temporal confounding in LS asthmatics. There was no confounding of PM_{10} or O_3 effects by either maximum temperature or minimum or average relative humidity. There were no effects of wind speed using any averaging time on symptoms in either LS or MS asthmatics (all p-values >0.4). Also, there was no significant interaction between O_3 and PM_{10} ($p<0.4$).

Multiplicative interaction of follow-up symptom classification (LS or MS) with each air pollutant variable was tested in regression models including all subjects. A steeper slope in LS asthmatics was suggested for both O_3 expressions (z scores around 1.50), current day 24-hr PM_{10} (z score 1.36), and both 5-day 8-hr and 24-hr PM_{10} (z scores around 1.2). Other PM_{10} expressions had z scores for interaction terms <0.7.

The robustness of the above models was retested accounting for fungal particles. For an increase from the minimum to 90th percentile of fungi (see Table 2) among MS asthmatics, the OR for the prior 24-hr average fungi was 1.43 (CI, 1.07–1.90), and the OR for the prior 12-hr daytime fungi was 1.34 (CI, 0.95–1.90), controlling for day-of-week trends. Similar effect levels were found in LS asthmatics for both the prior 24-hr average fungi (OR = 1.35; CI, 0.89–2.03) and 12-hr daytime fungi (OR = 1.35; CI, 0.96–1.89). There was no evidence that outdoor fungi confounded effects of any of the PM_{10} or O_3 variables in either MS or LS asthmatics.

The lack of a significant effect of O_3 in MS asthmatics was reevaluated given the influence of 4 MS asthmatics on O_3 parameter estimates involving the whole cohort of 24 subjects (discussed above). A model with these 4 subjects showed large and highly significant ORs for 1-hr O_3 (5.31; CI, 4.54–6.22) and 8-hr O_3 (3.64; CI, 2.41–5.51), in contrast to models with the other 6 MS asthmatics (ORs ~0.8). Associations with PM_{10} variables were also stronger and significant in these 4 subjects.

We then examined symptom–pollutant relationships in pediatric LS asthmatics who were on regularly scheduled doses of anti-inflammatory medications (seven subjects) versus those who were not (seven subjects). Five of the subjects taking anti-inflammatory medications were on inhaled corticosteroids and two were on cromolyn. Table 6 shows the results of separate regression models for the two LS asthmatic groups. A dramatic difference emerged, suggesting effect modification by anti-inflammatory medications for both PM and O_3. Findings for single pollutant models are as follows. Positive associations are shown with current day 8-hr and 24-hr PM_{10} in both groups, but ORs and significance levels are greater in subjects not on anti-inflammatory medications. Effects of current day 1-hr PM_{10} are suggested only in subjects not on anti-inflammatory medications and are smaller than effects of longer PM_{10} averaging times. The only significant lag PM_{10} effect in subjects on anti-inflammatory medications was the 8-hr maximum 2 days before the symptom report (OR 1.64; CI, 1.13–2.37). No combination of lags was significant (see Table 6, 5-day averages). Adverse effects of lagged PM_{10} were more clearly suggested in subjects not on anti-inflammatory medications, with 1-day, 3-day, and 4 day lags showing positive associations. The 5-day moving average of PM_{10} had the largest parameter estimates, which were significant for all averaging times. Relative effects of the 5-day PM_{10} variables were 8-hr >1-hr >24-hr. The 8-hr maximum PM_{10} expression showed an unusually strong association with asthma symptoms. There was a significant ($p<0.0005$) 10-times increase in risk of symptoms in asthmatics not on anti-inflammatory medications at the 90th percentile of daily 8-hr PM_{10} (59 µg/m^3). Also, the effects of current day O_3 are entirely isolated to asthmatics not on the anti-inflammatory medications (1-hr maximum O_3 $p<0.002$), and effect magnitudes are double that of regressions for all 14 LS asthmatic children in Table 5 (ORs ~4 vs. 2). The only suggested lagged O_3 effects were for 2-day lags in relation to symptoms in subjects on anti-inflammatory medications (OR = 2.41; CI, 1.26–4.61). Co-regressing 2-day lags of both 8-hr O_3 and 8-hr PM_{10} (see above OR) reduced effect estimates from single pollutant models (OR = 1.87 and 1.40, respectively; both $p<0.1$).

In the co-pollutant models presented in Table 6, subjects on anti-inflammatory medications showed nearly the same effects of current day 8-hr and 24-hr PM_{10} (controlling for current day 1-hr O_3) and O_3 did not improve model fit over PM alone. However, for subjects not on anti-inflammatory medications, ORs for current day PM_{10} were all

Table 5. Odds ratios (ORs) or asthma symptoms[a] in pediatric asthmatics in relation to 90th percentile increases in PM_{10} and O_3 concentrations: dependence on asthma symptom frequency[b] and pollutant averaging times in the Alpine, California, Panel Study, 1 August–30 October 1995

Air pollutant variable	Air pollutant range (minimum to 90th percentile)[c]	ORs (CI) per increase to 90th percentile concentration of PM_{10} or O_3: Single pollutant models[d]	Models adjusting for co-pollutant[e]
Less symptomatic asthmatics			
Current day PM_{10}			
1-hr max	47	1.38 (0.76–2.50)	1.10 (0.58–2.08)
8-hr max	36	2.18 (0.99–4.79)	1.77 (0.85–3.71)
24-hr mean	25	2.47 (1.23–4.95)**	2.08 (1.12–3.83)*
5-Day moving average PM_{10}			
1-hr max	47	2.70 (0.71–10.24)	2.40 (0.68–8.53)
8-hr max	36	4.84 (1.21–19.42)*	3.97 (1.09–14.54)*
24-hr mean	25	4.03 (1.22–13.33)*	3.35 (1.06–10.51)*
Current day O_3			
1-hr max	58 ppb	2.15 (1.04–4.44)*	1.76 (0.66–4.73)
8-hr max	46 ppb	1.92 (0.97–3.80)	1.51 (0.65–3.49)
More symptomatic asthmatics			
Current day PM_{10}			
1-hr max	47	2.24 (1.46–3.46)#	2.18 (1.46–3.27)#
8-hr max	36	1.82 (1.18–2.81)**	1.74 (1.15–2.63)**
24-hr mean	25	1.50 (0.80–2.80)	1.40 (0.77–2.53)
5-Day moving average PM_{10}			
1-hr max	47	2.18 (1.01–4.72)*	2.20 (1.02–4.76)*
8-hr max	36	2.25 (1.16–4.38)*	2.21 (1.16–4.18)*
24-hr mean	25	1.95 (1.12–3.43)*	1.87 (1.11–3.13)*
Current day			
1-hr max	58 ppb	1.25 (0.75–2.08)	1.16 (0.71–1.88)
8-hr max	46 ppb	1.22 (0.81–1.86)	1.16 (0.73–1.83)

Abbreviations: CI, 95% confidence interval; max, maximum.

[a]The asthma symptom severity score was dichotomized to no symptoms or symptoms not bothersome versus symptoms bothersome or interfering with daily activities.

[b]Less symptomatic asthmatics were defined as having <20% of days with asthma symptoms that were bothersome or interfered with daily activities during follow-up (14 asthmatics, 1,052 person-days of O_3 observations, 838 person-days of PM_{10} observations); more symptomatic asthmatics were defined as having ≥20% of days with asthma symptoms that were bothersome or interfered with daily activities (10 asthmatics, 707 person-days of O_3 observations, 607 person-days of PM_{10} observations).

[c]Values shown are µg/m^3 except where indicated.

[d]Single pollutant models involve 71 days for PM_{10} and 91 days for O_3 models; there was no confounding by weather, and models for more symptomatic asthmatics adjust for day-of-week trends.

[e]All PM_{10} models adjust for current day 1-hr maximum O_3; O_3 models for less symptomatic asthmatics adjust for current day 24-hr PM_{10}; O_3 models for more symptomatic asthmatics adjust for current day 1-hr maximum PM_{10}. All co-pollutant models are for 71 days with nonmissing PM_{10} data; therefore, single pollutant O_3 models are not strictly comparable.

*$p<0.05$; **$p<0.01$; #$p<0.001$

Table 6. Odds ratios (ORs) for asthma symptoms[a] among pediatric asthmatics in relation to 90th percentile increases in PM_{10} and O_3 concentrations: effect modification by anti-inflammatory medication use in less symptomatic subjects[b]; Alpine, California Panel Study, 1 August–30 October 1995

		ORs (CI)[d] per increase to 90th percentile concentration of PM_{10} or O_3	
Air pollutant variable	Air pollutant range (minimum to 90th percentile)[c]	Asthmatics on anti-inflammatory medications[e]	Asthmatics not on anti-inflammatory medications[f]
Single pollutant models			
Current day PM_{10}			
1-hr max	47	1.15 (0.50–2.70)	1.97 (0.94–4.11)
8-hr max	36	2.08 (0.70–6.22)	3.04 (1.05–8.83)*
24-hr mean	25	2.53 (0.96–6.65)	2.82 (1.26–6.28)*
5-Day moving average PM_{10}			
1-hr max	47	1.51 (0.18–12.71)	5.94 (1.63–21.52)**
8-hr max	36	2.96 (0.32–27.05)	9.66 (2.80–33.21)#
24-hr mean	25	3.50 (0.50–24.53)	4.56 (1.76–11.85)#
Current day O_3			
1-hr max	58 ppb	1.20 (0.46–3.15)	4.14 (1.71–10.00)#
8-hr max	46 ppb	1.11 (0.55–2.21)	3.59 (1.37–9.40)**
Co-pollutant models[g]			
Current day PM_{10}			
1-hr max	47	1.08 (0.48–2.41)	1.44 (0.60–3.47)
8-hr max	36	2.08 (0.83–5.22)	2.18 (0.78–6.09)
24-hr mean	25	2.55 (1.11–5.89)*	2.00 (1.01–3.97)*
5-Day moving average PM_{10}			
1-hr max	47	1.44 (0.19–10.78)	5.08 (1.44–18.00)*
8-hr max	36	2.83 (0.26–22.51)	6.67 (1.97–22.59)#
24-hr mean	25	3.42 (0.54–21.60)	3.20 (1.30–7.84)*
Current day O_3			
1-hr max	58 ppb	0.97 (0.30–3.15)	3.93 (0.77–20.06)
8-hr max	46 ppb	0.94 (0.45–1.97)	3.00 (0.59–15.16)

CI, 95% confidence intervals.
[a]The asthma symptom severity score was dichotomized to no symptoms or symptoms not bothersome versus symptoms bothersome or interfering with daily activities.
[b]Less symptomatic asthmatics were defined as having <20% of days with asthma symptoms that were bothersome or interfered with daily activities during follow-up.
[c]Values shows are μg/m³ except where indicated.
[d]Single pollutant models involve 71 days for PM_{10} and 91 days for O_3 models. Co-pollutant models are for 71 days with nonmissing PM_{10} data; therefore, single pollutant O_3 models are not strictly comparable. There was no confounding by weather or day-of-week trends.
[e]This includes seven subjects, five on inhaled corticosteroids and two on cromolyn, with 533 person-days of O_3 observations and 424 person-days of PM_{10} observations.
[f]This includes seven subjects with 519 person-days of O_3 observations and 414 person-days of PM_{10} observations.
[g]All PM_{10} models adjust for current day 1-hr maximum O_3; all O_3 models adjust for current day 24-hr PM_{10}.
*$p<0.05$; **$p<0.01$; #$p<0.001$.

reduced by 27–29% and standard errors (SEs) are inflated (only 24-hr PM_{10} is still significant). There is a similar finding for the 5-day average PM_{10} variables, but they remain significant. Also, for subjects not on anti-inflammatory medications, current day O_3 is not significant in co-pollutant models (controlling for current day 24-hr PM_{10}), but the ORs are similar to single pollutant O_3 models. Again, the regression with O_3 alone was rerun, restricted to the 71 days. One-hour O_3 showed a somewhat higher OR (4.65) than the co-pollutant model (3.93), although it was also not significant ($p<0.07$). A similar difference was found for the effect of 8-hr O_3 in a 71-day model (OR = 3.68; $p<0.11$) compared with the co-pollutant model (OR = 3.00). The restriction to fewer days, therefore, partly explains a lack of statistical significance in the co-regression. The effect of current day 1-hr O_3 was also retested by co-regressing with the 5-day average of 8-hr PM_{10} and the OR for O_3 increased (4.24; $p<0.1$).

There was no confounding of PM_{10} or O_3 effects by day of week, maximum temperature, or minimum or average relative humidity for either of the two groups (on or not on anti-inflammatory medications). There were no effects of wind speed using any averaging time on symptoms in either group (all p-values >0.4). An interaction term for O_3 and PM_{10} did not improve the fit of the above models (deviance difference <2.0).

Again, the robustness of the above models in the two groups was retested accounting for fungal particles. For LS asthmatic children taking anti-inflammatory medication, there was no effect of fungi ($p>0.6$). In contrast, there were significant effects of fungi on asthmatic children not taking anti-inflammatory medication. For an increase from the minimum to 90th percentile of fungi (see Table 2), the OR for the prior 24-hr average fungi was 1.70 (CI, 1.03–2.78), and the OR for the prior 12-hr daytime fungi was 1.61 (CI, 1.05–2.46). Fungal particles did not confound effects of any PM_{10} or O_3 variable, and the significant pollutant variables remained significant.

Multiplicative interaction between the use of anti-inflammatory medications and each air pollutant variable was tested in regression models including all LS subjects. A steeper slope in asthmatics not taking anti-inflammatory medications was suggested for both O_3 expressions (z scores around 1.80) and fungal spores (z score 1.60). Slopes were also steeper in asthmatics not taking anti-inflammatory medications for PM_{10} variables, but z scores were only around 1.0.

Cromolyn and nedocromil have different mechanisms of action and are less potent and effective anti-inflammatory medications than inhaled corticosteroids (*8*). Therefore, models were retested dropping the two LS asthmatics on these medications and retaining five subjects on inhaled corticosteroids. The only change was a decrease in the effect of current day 24-hr PM_{10} and a loss of significance (OR = 2.12; CI, 0.53–8.44). Remaining models showed no pollutant association as in models including the seven on any anti-inflammatory medication.

To test the linearity of associations for all of the above analyses, higher pollutant days were dropped and models were retested. For O_3, 5 days with over 120 ppb 1-hr maximum (the previous NAAQS) and the same 5 days with over 100 ppb 8-hr maximum were dropped and models were retested. This was repeated dropping the highest 10% of days (110 ppb 1-hr maximum and 90 ppb 8-hr maximum) and dropping the 25 days over the new 8-hr standard of 80 ppb O_3. Associations disappeared below the 120 ppb threshold in the models including the whole group and in MS asthmatic models ($p>0.4$), but O_3 was still associated with symptoms below 120 ppb in the four sensitive MS asthmatics (ORs = 2.57–3.77), but not below 100 ppb. Effects were also found at lower O_3 levels for LS asthmatics, with effect magnitudes that were relatively unchanged (days <110 ppb maximum O_3, OR = 2.54; CI, 0.93–6.94). Although dropping 25 days with over 80 ppb 8-hr maximum led to a nonsignificant parameter estimate ($p<0.14$), the slope was still positive (OR = 4.20). Lower concentration effects were also evident in LS asthmatics not on anti-inflammatory medications, including the model excluding days with over 80 ppb 8-hr maximum O_3 ($p<0.005$). This suggests a linear dose–response relationship for O_3 and symptoms in the most sensitive subjects, but a possible threshold in other subjects. For the PM_{10} variables, the highest 10% of days was dropped and models were retested. For all models, parameter estimates were either unchanged or actually increased, and they often remained statistically significant if so for above models including all observed days. For example, in the model that included all asthmatics, dropping 10% of days above 77 μg/m^3 for current day 1-hr maximum PM_{10} led to an OR of 1.89 (CI 1.20–2.98). The effects of the 5-day moving average for 8-hr maximum PM_{10} below 53 μg/m^3 in LS asthmatics not on anti-inflammatory medication was reduced to an OR of 2.77 (p<0.14). Overall, however, these results suggest a linear dose–response relationship for PM_{10} and symptoms.

Discussion

Overview of Findings

The present findings are consistent with other recent asthma panel studies conducted with diverse populations of children that found adverse effects on daily asthma severity by PM_{10} and O_3 in warm periods and by PM_{10} in winter (*20–26*). Panel studies focusing on adult asthmatics have also found adverse effects of air pollution on daily asthma severity (*27–29*). Multiday moving averages of PM_{10} had greater effects than single day expressions in the studies examining such variables, which is consistent with the present findings. The present study adds to previous findings because it is the first to report particle effects from 1-hr and 8-hr maximum PM_{10} as compared with the standard metric of 24-hr means. We also show informative differences in the strength of symptom–pollutant associations between groups of asthmatics stratified on their level of daily asthma symptom frequency and on anti-inflammatory medication use. Outdoor fungal particles were also significantly associated with asthma symptoms, but did not confound effects of either PM_{10} or O_3, which is consistent with our previous studies (*15,18*). Our findings are summarized below. In most cases, the ordering of relative magnitudes of association for the various pollutant variables is imprecise because their confidence intervals overlap markedly (see tables). We present the ordering as a point of discussion to generate hypotheses and to prompt others to replicate or refute the relative strengths of association.

- In the whole group of 24 pediatric asthmatics, relative effect magnitudes across the different pollutants and averaging times for current day measurements were 1-hr PM_{10} ≅ 8-hr PM_{10} >1-hr O_3 ≅ 8-hr O_3 ≅ 24-hr PM_{10}, with the tightest confidence intervals and most robust associations in co-pollutant models being for 1-hr and 8-hr maximum PM_{10} (Table 4).
- There were notable differences in pollutant effects between 14 less versus 10 more symptomatic asthmatics (Table 5): 1) associations with current day O_3 were found only in LS asthmatics, but four MS asthmatics showed strong O_3 effects in contrast to the remaining six; 2) relative effect magnitudes across PM_{10} averaging times for current day measurements were inversely ordered for LS versus MS asthmatics (LS asthmatics: 24-hr >8-hr >1-hr PM_{10}; MS asthmatics: 1-hr >8-hr > 24-hr PM_{10}); and 3) relative effect magnitudes across PM_{10} averaging times for 5-day moving averages were also different, with larger effects for all averaging times in LS asthmatics (LS asthmatics: 8-hr >24-hr >1-hr PM_{10}; MS asthmatics: 1-hr ≅ 8-hr >24-hr PM_{10}).
- Among the LS asthmatics, there was evidence of effect modification by anti-inflammatory medication use (Table 6): 1) associations with current day O_3 were found only in those not on anti-inflammatory medications, and effect sizes were nearly three times those found in the models involving all subjects (OR ~4.0 versus 1.5); 2) relative effect magnitudes for current day PM_{10} were similar between groups on or off medication, reflecting results for the combined LS group (8-hr ≅ 24hr >1-hr PM_{10}); but, there were no PM_{10} effects in subjects on corticosteroids; 3) there were no 5-day PM_{10} effects in subjects on anti-inflammatory medications, but significant and large effects were found in those not medicated (for 5-day PM_{10}, 8-hr >1-hr >24-hr PM_{10}; 90th percentile ORs were 6.67, 5.08, and 3.02, respectively, adjusted for O_3); and 4) among LS asthmatics, there was no effect of outdoor fungi in subjects taking anti-inflammatory medication, whereas in unmedicated subjects the significantly adverse effect of fungi was enhanced in comparison to the whole panel (24-hr average fungi, ORs 1.70 versus 1.36, respectively).

Effects of Particles

To our knowledge, this is the first paper to show the potential importance of peak (1-hr and 8-hr) PM_{10} exposures to adverse respiratory effects of particles in an epidemiologic study. There are no published experimental studies to our knowledge that have directly examined the issue of differences in particle effects by concentration × time exposure profile for a single administered dose. In general, we found larger associations with asthma symptoms for 1-hr and 8-hr maximum PM_{10} exposures, as compared with the standard metric of 24-hr average PM_{10}. This was found with effects of current day PM_{10} in the subpopulation of MS asthmatics (Table 5) and with effects of 5-day PM_{10} in LS asthmatics not on anti-inflammatory medications (Table 6). Among the seven LS asthmatics not on anti-inflammatory medications, the 5-day moving average of 8-hr maximum PM_{10} was associated with a 10 times higher risk of adverse asthma symptoms (seven times higher adjusted for O_3) at the 90th percentile of 8-hr PM_{10} (59 μg/m^3) relative to the minimum pollution day (23 μg/m^3; p<0.0005) (Table 6). This suggests that there may be a subgroup of asthmatics who potentially are very susceptible to daytime excursions of particulate air pollution.

The mechanism of particle effects in some of the LS asthmatics may have been more dependent on cumulative exposures (as represented by 5-day moving averages), leading to more gradual inflammatory responses. In contrast, effects in some of the MS asthmatics could have been mediated more by short-term (current day) peak exposures, leading to more immediate bronchoconstrictive and inflammatory responses similar to aeroallergen effects involving immediate and late phase bronchospastic reactions (4–6 hr later) induced by an initial IgE-mediated response (*30*). Differences in medication use in the two groups, particularly anti-inflammatory medications, may have also modified responses to air pollutants. Another possibility is that differences between averaging times could be due to interindividual differences in the relevance of outdoor stationary site PM_{10} to personal particle exposures. Given that the strongest effects were for 8-hr exposures over the current and previous 4 days, it is possible that maximal personal exposures occurred around the same 8-hr time period from late morning to early evening. This is a time when many children are outdoors and physically active.

Other investigators have similarly explained stronger effects from 5-day moving averages. In a study of a nonstratified group of asthmatic children living in Amsterdam (*24*), adverse effects on lower respiratory symptoms were also found for similarly low 5-day mean concentrations of 24-hr PM_{10} (symptom prevalence difference between the highest day, 60 μg/m^3, vs. the lowest day, 16 μg/m^3, relative to the mean prevalence was 1.47; CI, 1.00–1.94). Smaller effects for current day 24-hr PM_{10} were found (1.23; CI, 0.92–1.54). This led authors to hypothesize that cumulative (long-term averaged) exposure variables are less affected by exposure misclassification due to temporally variable differences in personal exposures because variation in exposure estimates are averaged out.

We did not expect that asthma symptoms would be strongly associated with the low levels of particles in Alpine, California (all observations <109 μg/m^3 for hourly

PM_{10}). In regression models involving subpopulations of children incorporating both PM_{10} and O_3, the effects of PM_{10} variables were usually still statistically significant and only reduced in magnitude in LS asthmatic children. These findings suggest that the irritant potential of PM_{10} at inversion layer elevations may be considerably greater than expected based upon mass. This supports the view that considerable scientific work is required to determine the causal components of particles, components that may have adverse effects at low mass concentrations (e.g., the ultrafine particle fraction, polycyclic organic compounds, metals, etc.). The relevant particle toxicities (in this region at least) appear to be largely independent of O_3, suggesting an important role in particle effects by primary combustion products, which in Southern California are primarily from automobile exhaust.

Effects of Ozone

The findings of the present study support the view that asthmatics may be a group particularly sensitive to the adverse respiratory effects of trophospheric O_3 (*31*). Recent evidence suggests that a major mechanism for this may be the effect of O_3 on airway inflammation (*6*), in addition to less notable effects on acute lung function responses, possibly neurally mediated (*32*). This evidence was found in an experimental chamber study of 18 asthmatic and 81 normal adult subjects exposed to 197 ppb O_3 over 4 hr, with 50 min/hr of treadmill exercise (*6*). There were no differences between the groups in the significant O_3-induced deficits in forced expiratory volume in 1 sec (FEV_1) or in forced vital capacity (FVC). However, a nonsignificant trend of increased specific airway resistance (sRaw) was noted in asthmatics versus normal subjects. Also, two inflammatory markers (percentage of neutrophils and total protein concentration) in BAL fluid were significantly increased in asthmatics 18 hr following O_3 exposure as compared with 20 normal subjects undergoing BAL. These changes were not correlated with decrements in FEV_1 or FVC, but were significantly correlated with sRaw. Scannell et al. (*6*) concluded that O_3-induced changes in sRaw could reflect airway inflammation, possibly mediated through a decrease in airway caliber from mucosal edema. These findings are supported by other experimental studies in humans showing evidence of O_3-induced inflammation in BAL fluid (*33–36*). Our epidemiologic findings are consistent with these experimental results because of the near tripling of O_3 response magnitude among LS asthmatic children not taking anti-inflammatory medications, compared with the whole group, and the lack of response in medicated LS asthmatics.

The finding that subjects on anti-inflammatory medications showed no effect of O_3 is countered somewhat by another epidemiologic study (*37*). In that recent study of 166 asthmatic children attending one of three week-long asthma summer camps, 71% regularly used inhaled anti-inflammatory medications. There was a significantly increased risk of an asthma exacerbation (RR = 1.4) and of experiencing chest symptoms (RR = 1.4) on the highest pollution day (O_3, 160 ppb) versus the average day (O_3, 84 ppb). Higher O_3 levels were found in that study, with the previous NAAQS of 120 ppb 1-hr O_3 being exceeded on 25% of the study days, versus only 5% in the present study.

The effects of O_3 in the LS but not MS asthmatic group are informative. The relative lack of O_3 effects in models including all 10 pediatric MS asthmatics is unexpected because only one of these subjects was taking an anti-inflammatory medication. However, when a model was tested including the 4 MS asthmatics found to influence O_3 parameters in the whole group analysis, significant and strong associations were found for O_3 (1-hr O_3, OR = 5.31; $p<0.00005$). It is possible that for the MS asthmatics not showing an O_3 effect, their greater symptom severity during follow-up as compared with the LS asthmatics was due to other exposures unrelated to O_3. For example, indoor allergens may have driven their day-to-day symptom variability. It is also possible that these MS asthmatics may have avoided being outdoors and/or avoided outdoor physical activity, with an attendant lowering of potential delivered O_3 dose given the low indoor/outdoor O_3 ratio (around 0.3) (*38*) and decreased minute ventilation.

Relevance to EPA Air Pollution Standards

The Alpine governmental monitoring station is part of the nationwide EPA network. On only 2 of the days monitored (every sixth day) between 1981 to 1985 did levels of total suspended particulates (including 10–50 μm particles) exceed the old federal standard of 260 $\mu g/m^3$, after which governmental monitoring for particulates was discontinued. This is in contrast to O_3 levels, which are historically the highest in San Diego County. We originally had little expectation of particle effects. In our previous report on 22 asthmatics followed in Alpine during the spring of 1994, we found no association between ordinal asthma symptoms and either O_3 or 24-hr average TEOM PM_{10}, despite similar pollutant levels (*15*). There were modest associations between as-needed β-agonist inhaler use (a surrogate of symptom severity) and 24-hr PM_{10}. Some critical irritant characteristics of the particles could have differed between then and the fall 1995 period. More importantly, there was no stratification of subjects similar to the present report and no analysis of binary symptom scores. A reanalysis of that data is planned.

The EPA's previous NAAQS for particulate air pollution was set at a 24-hr average PM_{10} concentration of 150 $\mu g/m^3$. The EPA has recently revised the NAAQS for particulate air pollution that centers on adding a new primary $PM_{2.5}$ standard of 50 $\mu g/m^3$ 24-hr daily average concentration. The new $PM_{2.5}$ standards make it likely that more U.S. regions will exceed that NAAQS, but the EPA is retaining the previous PM_{10} standard with less stringent attainment criteria. Because the maximum day's 24-hr PM_{10} was only 42 $\mu g/m^3$, it is extremely unlikely that the new $PM_{2.5}$ standard was ever exceeded during the study period. This means that particle effects may be determined by factors not entirely dependent on mass and/or that setting standards based on 24-hr averages will miss important short-term excursions during peak exposure periods. This could further explain the lack of particle effects on symptoms in the 1994 study (*15*) because we did not examine peak PM_{10}.

The EPA is also tightening the NAAQS for O_3 to an 80 ppb 8-hr maximum daily concentration from the previous 120 ppb 1-hr standard. Therefore, it is of current relevance that in this study the 1-hr maximum O_3 showed slightly stronger effects than the 8-hr averaging time. Findings may differ when accounting for outdoor activity profiles because the maximal exposure in the afternoon is also the time of highest hourly O_3 levels. Although the 8-hr average was slightly less informative in this analysis, the effects found suggest that the new NAAQS would probably afford better protection of the susceptible asthmatic population than the current one. The reason is that the previous NAAQS of 120 ppb 1-hr maximum O_3 was only exceeded 5 times, whereas the new NAAQS of 80 ppb 8-hr maximum O_3 was exceeded 25 times.

Implications for Future Research

A key strength of the present findings is that the measure of asthma symptom severity we use accounts for some aspects of daily well-being as assessed by the individual. Additional research should incorporate similar approaches to asthma outcome assessment. The present finding of major differences in air pollution effects between asthmatics with less versus more frequent asthma symptom episodes during follow-up is directly dependent on the symptom scoring approach. The classification is also based on daily longitudinal data, which is expected to yield a more accurate description of an individual's asthma severity than historical questionnaire data.

The design of the present study made it possible to find informative differences in air pollutant effects on small subgroups of asthmatic children. As discussed above, the repeated measures design can yield powerful analyses with large sample sizes (person-days) for small numbers of subjects. The limitation with smaller numbers of subjects is that it is more difficult to generalize results to asthmatics as a group or to asthmatics with the characteristics of the subpopulations presented herein. To this end, larger panel studies are needed in diverse populations to examine the types of host susceptibility suggested by the present subgroup analyses. Additional work is also needed to quantify asthma severity according to symptom reports (e.g., repeated spirometry). For instance, some asthmatics appear to be poor perceivers of bronchoconstriction, particularly those with chronic airflow obstruction (*39*), while others may over-report symptom severity.

The results presented support the hypothesis that current day hourly peak PM_{10}, as well as multiple-day cumulative average exposures using 8-hr PM_{10} maximums, may be more informative in explaining observations of adverse particle effects on acute asthma severity than current or multiple-day 24-hr average PM_{10} exposures. It is possible, for instance, that outdoor peaks in PM_{10} are better surrogates for personal outdoor exposures during the daytime, exposures that can often occur at times of high physical activity leading to greater particle doses. Confirmation of this will require research incorporating real time PM sampling and personal particle exposure assessments. In addition, relative effects of PM_{10} and O_3 may differ in subgroups of asthmatics depending on their current disease severity. For example, it is expected from experimental data that particle deposition and retention is greater in the airways of more severe as compared with milder asthmatics (*40*). As evidenced in this paper, acute responses to the delivered dose are likely to be further modified by anti-inflammatory medication use. Additional evidence for the biological plausibility and consistency of the associations presented here is expected to advance understanding of the determinants of susceptibility to adverse effects of air pollutants, including short-duration exposure to high particle excursions.

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